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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,509	10/18/2005	Mitsuharu Hirai	TOYA114.010APC	4683

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,509	HIRAI, MITSUHARU	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2007 has been entered. Claims 1, 2, 7 and 8 have been amended. Claims 1-9 are pending and addressed below.

Previous Rejections

2. The prior art rejections under 35 USC 103(a) are withdrawn in view of the new ground(s) of rejections necessitated by applicants amendment of the claims.

New Ground(s) of Rejections

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lander et al (WO 98/20165, May 1998) in view of Buck et al (Biotechniques, vol. 27, no. 3, pages 528-536, 1999) and further in view of Hiratsuka et al (cited on IDS filed 7/2006). Regarding claims 1-2 and 7-8, Lander et al teach a nucleic acid probe and kit (pages 4-5 and 27-28), wherein the nucleic acid probe is isolated from a sequence that is 100% identical to the sequence of SEQ ID NO: 2 (see page 292, "ESTD-B3AR", second line of the sequence). Lander further teaches a sequence comprising a sequence that is 100% identical to the nucleotide sequence of SEQ ID NO: 8 (see page 292, "ESTD-B3AR", second line of the sequence).

Lander et al do not expressly teach that the probe nucleotide has a nucleotide sequence ending at the nucleotide number 196 in the nucleotide sequence of ESTD-B3AR.

Lander et al also do not teach wherein 3' end of the nucleic acid is labeled with a fluorescent dye in which the fluorescence of the fluorescent dye decreases upon hybridization.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed nucleic acid probe simply represent a structural homolog of the oligonucleotides taught by Landers et al, which are 100% derived from sequences expressly suggested by the prior art of and known in the prior art as disclosed by Landers et al as useful for primers and probes for the detection of polymorphism, such as in the *Beta*-3 adrenergic receptor (ESTD-B3AR), and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA

1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck et al expressly provides a general teaching of evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers or probes would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Buck does not teach wherein 3' end of the nucleic acid is labeled with a fluorescent dye in which the fluorescence of the fluorescent dye decreases upon hybridization.

Hiratsuka et al provides a general teaching of labeling nucleic acid probes at one end with a fluorescent dye, wherein said dye decreases upon hybridization and wherein the label is located at the 3' end (see Table 1). Hiratsuka teaches that theses probes are useful for detecting single nucleotide polymorphism (col. 1, third paragraph of col. 1). Hiratsuka et al teach that a probe labeled with a fluorescent dye that decreases during hybridization allows one to analyze single-base mutations based on its characteristic Tm during melting curve analysis (page 39, col. 1, last paragraph and page 37, col. 2, last paragraph). Additionally, Hiratsuka et al teach that such nucleic acid probes can be used in methods that allow rapid, highly sensitive and high-throughput analysis of single nucleotide polymorphisms (page 39, last paragraph of col. 2 and abstract).

Therefore, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the nucleic acid probe of Lander et al in view of Buck et al to encompass a fluorescent compound, such as a fluorescent dye located at the 3'-end which decreases during hybridization as taught by Hiratsuka et al for the obvious benefit of analyzing single base mutations in a rapid, highly sensitive and high-throughput manner as suggested by Hiratsuka.

With regards to claim 3, Hiratsuka et al teach a method of detecting a mutation comprising a melting curve analysis for a nucleic acid having a single nucleotide polymorpshim site by using a nucleic acid probe labeled with a fluorescent dye, wherein the single nucleotide polymorphism is a mutation in a nucleotide sequence in a nucleic acid encoding a beta2-adrenergic receptor (abstract, page 36, third paragraph of col. 1;

page 37, section 2.4, 3.1; see also "Discussion"). Landers in view of Buck teaches a nucleic acid probe as defined by the claim 1.

With regards to claims 4 and 5, Landers et al teach wherein a region containing the single nucleotide polymorphism site in a nucleic acid contained in a sample is amplified to obtain the nucleic acid showing the single nucleotide polymorphism by a method using a DNA polymerase (see 11-14 and Examples at page 28-29).

With regards to claim 6, Hiratsuka et al teach wherein a real-time PCR reaction is performed wherein the amplification is performed in the presence of a nucleic acid probe to analyze the single nucleotide polymorphism (page 37, section 2.4).

With regards to claim 9, Landers et al teach primer for amplifying the region containing the mutation (see Examples at page 28-29 and page 292 for targeted polymorphic region). Hiratsuka et al further supports amplification of target specific regions of a nucleic acid sequence.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Patent Examiner
Art Unit 1637